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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,441	03/01/2006	Soren Persson	SSI7USA	7400

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EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,441	PERSSON ET AL.	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 39-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 39-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/15/08,6/15/06, 4/12/06* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. The amendment filed September 15, 2008 has been entered. Claims 1, 39-40, 43 and 47-50 have been amended. Claims 2-38 are cancelled. Claims 1 and 39-60 are under consideration in this office action.

Election/Restrictions

2. The election/restriction of June 19, 2008 is withdrawn in view of applicants' amendments to the claims.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on September 15, 2008, June 15, 2006 and April 12, 2006 were filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

4. Claim 1 is objected to because of the following informalities: Acronyms like A/EEC, EPEC, ETEC, VTEC and EIEC must be spelled out when used for the first time in a chain of claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1 and 39-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) The claims are drawn to a screening method for simultaneous detection of diarrheagenic *Shigella* species and *E. coli* (DEC) including A/EEC & EPEC, ETEC, VTEC, EIEC and strains with the *ehxA* gene, wherein said method comprises performing multiplex PCR with two or more primers in a single reaction, wherein the primers comprise at least one primer which specifically amplifies *exhA,* at least a second primer selected from a primer which specifically amplifies *vtx1* or a primer which specifically amplifies *vtx2,* and at least one primer which specifically amplifies a further gene selected from the group consisting of *ipaH, eae, sta* or *estA, vtx1, vtx2* and elt, at least one of the primers being selected from Table 3, and identifying subjects having amplified *exhA and vtx1* or *vtx2* genes. It appears that the claim requires a) at least one primer which specifically amplifies *exhA* and b) at least a second primer which specifically amplifies *vtx1* or *vtx2,* however it is unclear which genes, the phrase “and at least one primer which specifically amplifies a further gene selected from the group consisting of *ipaH, eae, sta* or *estA, vtxl, vtx2* and elt, at least one of the primers being selected from Table 3, and identifying subjects having amplified *exhA and vtxl* or *vtx2* genes" is intending to encompass.

For instance, does the phrase mean: c) at least one primer which specifically amplifies a further SINGLE gene selected from *ipaH, eae, sta* or *estA, vtxl, vtx2* and elt and a gene selected from Table 3; OR

c) at least one primer which specifically amplifies a further gene selected from the group consisting of 1) *ipaH, eae, sta* or 2) *estA, vtxl, vtx2* and 3) elt and a gene selected from Table 3; i.e., one gene selected from 1) or 2) and 3) or all three of the genes in 1) or 2); OR

if the method comprises: c) at least one primer which specifically amplifies a further gene selected from the group consisting of 1) *ipaH, eae, sta*, or *2) estA, vtxl, vtx2* and 3) elt, and d) at least one of the primers being selected from Table 3 OR something else. Therefore it is unclear what primers and which genes are included for the amplification and clarification is requested.

B) The preamble of the claims is drawn to a screening method for simultaneous detection of diarrheagenic *Shigella* species and *E. coli*. The claims do not require the sample to come in contact with the primers. There is no correlation step which correlates the screening method for simultaneous detection of diarrheagenic *Shigella* species and *E. col*i to identifying subjects having amplified *exhA* and *vtx1* or *vtx2* genes. Therefore, the goal of the preamble is not commensurate with the steps of the method to thereby allow detection of diarrheagenic *Shigella* species and *E. coli.*

C) Regarding claims 39, 40, 47 and 50, the phrase "such as" and “such as at least…” renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

D) A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 49 and 53 recite the broad recitation of at most 90 nucleotides, and the claim also recites at most 80, 70, 60, 50, 40 or 30 which is the narrower statement of the range/limitation.

E) Regarding claims 47 and 5, the phrase "preferable" or “preferably” renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1 and 39-43, 45-49, 54-57 and 59-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toma et al., (J. of Clin. Microbiol. 2003. Vol. 41(6): 2669-2671) in view of Grabowski et al., (WO 02/053771 published July 7, 2002; however the US Patent Application Publication US 2004/0110251 will be used as the English translation).

The claims are drawn to a screening method for simultaneous detection of diarrheagenic *Shigella* species and *E. coli* (DEC) including A/EEC & EPEC, ETEC, VTEC, EIEC and strains with the *ehxA* gene, wherein said method comprises performing multiplex PCR with two or more primers in a single reaction, wherein the primers comprise at least one primer which specifically amplifies *exhA,* at least a second primer selected from a primer which specifically amplifies *vtx1* or a primer which specifically amplifies *vtx2,* and at least one primer which specifically amplifies a further gene selected from the group consisting of *ipaH, eae, sta* or *estA, vtx1, vtx2* and elt, at least one of the primers being selected from Table 3, and identifying subjects having amplified *exhA and vtx1* or *vtx2* genes. The dependant claims are gene to the detection of specific genes; detection by electrophoresis; the sample source; and specific characteristics of the primer.

The claims are also drawn to a kit which comprises in a single or separate containers, nucleotide sequences which are able to prime amplify, in a nucleotide sequence amplification reaction the genes: *ipaH, eae, sta, vtx1, vtx2,* and elt or parts pf

these genes or the complementary strands to the genes or parts thereof and which comprises a control.

Toma et al., teach multiplex PCR assays for identification of human diarrheagenic *E. coli* (DEC), enteropathogenic *E. coli* (EPEC), Enteroinvasive *E. coli* (EIEC), enterotoxigenic *E. coli* (ETEC), enteroaggregative *E. coli* (EAEC) and *Shiga* toxin producing *E. coli* (STEC) (page 2269, col.1). Toma et al., selected as targets, *eae* for EPEC, *stx* for STEC, *elt* and *est* for ETEC, and *ipaH* for EIEC (page 2669, col.2). Toma et al., teach for each target, different primers were selected, see Table 2. Table 1 teaches the control strains and positive genes used in the study. Toma et al., teach the PCR products were electrophoresed on an agarose gel for visualization (page 2670, col.2). Table 3 shows the results of the PCR, including genes *eae, stx, ipaH, elt, est* and *aggR*. Toma et al., teach the practical and rapid diagnosis for identification of diarrheagenic *E. coli* (page 2671, col. 2). Toma et al., teach *E. coli* is the most important etiologic agent and the need to differentiate the organism from other nonpathogenic members to enable rapid detection of virulence (page 2669, col.1). However, Toma et al., do not teach amplification of *exhA, vtx1* or *vtx2* genes.

Grabowski et al., teach a multiplex PCR amplification reaction where more than two primers are used to simultaneously detect genes consisting of *SltI* (*vtx1*), *SltII* (*vtx2*), *eae* and *hlyA (exhA)* [para 0030]. Grabowski et al., teach VTEC is characterized as either possessing the Slt genes SltI and SltII are also designated vtx1 and vtx2 [para. 0043 and 0045]. Grabowski et al., teach that hlyA is also known in the art as hemolysin A; it is noted that the gene for hemolysin A is referred to as exhA in the instant

specification [para. 0047]. Grabowski et al., teach primers and probes that hybridize on the target or used fro the direct or indirect detection of the target [para. 0038 and 0040]. Grabowski et al., teach the oligonucleotides or combinations of the oligonucleotides in the form of a kit, wherein the kit also includes reagents for the detection [para. 0065]. Grabowski et al., teach detection of *E. coli* and *Shigella* [para. 0089]. Grabowski et al., teach detection of the amplicons can be by gel electrophoresis or the detection of DNA bands [para. 0092 and 0231]. Grabowski et al., teach detection by visual indication in agarose gel electrophoresis of multiplex mixtures [para. 0309]. Grabowski et al., teach a detection means by coupling a fluorescent molecule to the probe and achieving a probe-amplicon hybrid [para. 0093].

Grabowski et al., teach using foodstuffs or fecal matter as the sample [para. 0069 and 0233]. Grabowski et al., teach preferred oligonucleotide combinations for the detection of pathogenic E. coli, including VTEC, EHEC [Table after para. 0308]. Grabowski et al., teach SEQ ID NO:24 which has 32 base pairs; the sequence has 100% sequence identity to instant SEQ ID NO:16. Grabowski et al., teach incorrect positive classification can be avoided by using specific sequences [para. 0087]. Grabowski et al., teach carrying out E. coli control reactions simultaneously, ie, in the same reaction vessel together with the EHEC detection or in parallel [para. 0089].

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to combine the methods as taught by Toma et al., and Grabowski et al., and incorporate additional primers to amplify specific genes in order to provide a specific, practical and rapid diagnosis for identification of diarrheagenic

Shigella and E. coli. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods taught by Toma et al., and Grabowski et al., in the screening method for simultaneous detection and identification of subjects having amplified *exhA*, and *vtx1* or *vtx2* genes when both teach performing multiplex PCR with two or more primers in a single reaction for the identification of specific genes. Furthermore, all of the claimed elements were known and disclosed by Toma et al., and Grabowski et al, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Claim Rejections - 35 USC § 103

7. Claims 1 and 39-43, 45-49, 54-57 and 59-60 are rejected under 35 U.S.C. 103(a) Claims 44, 50-53 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toma et al., (J. of Clin. Microbiol. 2003. Vol. 41(6): 2669-2671) in view of Grabowski et al., (WO 02/053771 published July 7, 2002; however the US Patent Application Publication US 2004/0110251 will be used as the English translation) as applied to claims 1, 43 and 54 above, and further in view of Karube et al., (WO 98/50581, see also US Patent 6,391,546 for the English translation).

The claims are drawn to the screening method and kit using probe sequences from Table 7.

Toma et al., and Grabowski et al., have been discussed above however neither teaches the use of probe sequences from Table 7.

Karube et al., teach The invention relates to a method of detecting target nucleotide sequence (especially a DNA sequence). The method comprises converting the target sequence into a sequence in which part is two-stranded and the rest are single-stranded. The single-stranded part is then detected by hybridizing with its complementary sequence (e.g. with a complementary sequence immobilized on a surface plasmon resonance biosensor chip). The method utilizes asymmetric PCR for the detection. The method is used for detection of nucleotide sequences such as those specific to pathogenic microorganisms, including sequences coding for toxins of pathogenic strains of E. coli. The method is specific and highly sensitive. Karube et al., teach preferred oligonucleotide combinations for the detection of pathogenic E. coli. Karube et al., teach a sequence having 100% sequence identity to instant SEQ ID NO:32.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention to combine the methods as taught by Toma et al., and Grabowski et al., and incorporate additional probes as taught by Karube et al., to in order to provide a specific, practical and rapid diagnosis for identification of *E. coli*. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the methods taught by Toma et al., Grabowski et al., and Karube et al., in the screening method for simultaneous detection and identification of subjects having amplified *E.coli* genes when all the references teach performing PCR with a

variety of probes and primers in a reaction for the identification of specific genes. Furthermore, all of the claimed elements were known and disclosed by Toma et al., Grabowski et al, and Karube et al., therefore one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Conclusion

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi, can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645